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EXAMINER

SULLIVAN, DANIEL M

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1636

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/755,003

Applicant(s)

EGGAN ET AL.

Examiner

Daniel M Sullivan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 October 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-48 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-48 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 12.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

This Non-Final Office Action is a response to the "Amendment A" filed October 1, 2002 (Paper No. 11) in reply to the First Office Action on the Merits mailed March 21, 2002 (Paper No. 8). Claims 6, 7, 40, 41 and 44 were amended in Paper No. 11. Claims 1-48 are pending and under consideration in the application.

Response to Amendment

Claims 1, 5, 8, 11, 14, 18, 21, 40, 41 and 44 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claims.

Rejection of claims 7 and 41 under 35 U.S.C. § 112, second paragraph, is withdrawn in view of the amendments to the claims such that they are no longer indefinite.

Rejection of claim 40 under 35 U.S.C. § 112, second paragraph, is withdrawn in view of the amendments to the claim and clarification provided.

Rejection of claims 1-39 and 41 under 35 U.S.C. § 103(a) as being unpatentable over Wang *et al.* further in view of Rideout *et al.* is withdrawn.

Rejection of 42-48 under 35 U.S.C. § 103(a) as being unpatentable over Wang *et al.* and Uchida *et al.* further in view of Rideout *et al.* is withdrawn.

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Claims 1, 4, 8-13, 15, 21-26, 31-34, 38-40 and 44 are newly rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claims.

Claims 19, 20, 25, 26 and 47 are newly rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-48 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of copending Application No. 09/957,659.

Claims 1-3, 8-12, 14-16, 21-23, 27, 31, 33, 35, 38 and 41 are newly rejected under 35 U.S.C. § 102(b).

Claims 18, 19, 25, 27, 28, 35, 36 and 45 are newly rejected under 35 U.S.C. § 103(a).

Response to Arguments

Claim Rejections - 35 USC § 112

Rejection of claims 1, 5, 8, 11, 14, 18, 21 and 41 under 35 U.S.C. § 112, first paragraph.

The claims were rejected as lacking enablement for a method of producing any non-human mammal for reasons of record in Paper No. 8.

Applicant's arguments filed in Paper No. 11 have been fully considered but they are not persuasive.

In the first full paragraph on page 4, Applicant argues that the specification teaches methods of producing non-human mammals, citing teachings in the specification regarding production of non-human mammals by tetraploid blastocyst complementation (e.g. page 2, lines 12-15), in particular production by introducing non-inbred pluripotent cells into tetraploid blastocysts of the same mammalian species to produce an embryo and transferring the embryo to a foster mother (e.g. page 6, lines 2-10), the production of mutant non-human mammals by the preceding method (e.g. page 6, lines 17-22), and the production of non-human embryos by introducing non-inbred pluripotent cells into non human tetraploid blastocysts and maintaining the resulting tetraploid blastocysts under conditions that result information of embryos (e.g. page 9, line 28 to “page 9, line 2”; it is presumed that Applicant actually means page 10, line 2). Applicant also points out that methods for producing tetraploid blastocysts, for introducing non-inbred pluripotent cells into tetraploid blastocysts and for producing mutant non-inbred pluripotent cells were readily available at the time of filing.

Applicant further points out that the teachings of the specification were applied to the production of both non-mutant and mutant mice by tetraploid blastocyst complementation, and assert that “Applicants have thus demonstrated that both non-mutant and mutant non-human mammals are produced by tetraploid blastocyst complementation using non-inbred pluripotent cells when following the written disclosure” (third paragraph on page 5).

First, it should be pointed out that the claims have been rejected to the extent that they read on a method of producing a transgenic non-human mammal or transgenic mutant non-human mammal *other than* a transgenic mouse or transgenic mutant-mouse. As stated in the previous action, the claims are enabling for “a method of producing a transgenic mouse or

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transgenic mutant mouse” (Paper No. 8, page 3, paragraph 1). It is also important to point out that the teachings of the instant disclosure and prior art have only been reduced to practice in mice; therefore, teachings cited in Paper No. 11 and restated herein above, are merely prophetic as they are applied to all mammalian species other than mice. Thus, the issue at hand is whether the teachings of the specification and prior art provide sufficient guidance to enable the skilled artisan to practice the invention in any and all mammalian species without undue experimentation.

In Paper No. 8, the Examiner argues “[s]ince ES cell technology was required to produce the claimed animals and practice the claimed methods...in the absence of such [ES cell] technology available in other species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed animals and to practice...the claimed methods in species other than mice” (first paragraph on page 6).

In response, Applicant argues that the references cited by the Examiner fail to support the conclusion that undue experimentation would be required to practice the invention in species other than mice. With regard to Bradley *et al.*, Applicant concedes that the reference teaches that in 1992, it had yet to be demonstrated that ES cells isolated from farm animal species can proliferate and differentiate in an embryo *in vivo* and contribute to somatic tissues or germ cells, but argues Bradley *et al.* “do not conclude that the ES cells isolated from farm animal species are not ES cells or that ES cells cannot be isolated from mammalian species other than mice. In fact, Bradley *et al.* indicate that ‘ES cells offer the same potential advantages for genetic engineering of large animals that have been realized in mice’” (first full paragraph on page 6). However, practicing the methods of the instant invention, and producing animals according to those

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methods, requires more than possession of ES cells, it requires that the ES cells “proliferate and differentiate in an embryo *in vivo*”. Cells having all of the properties of an ES cell except for the ability to produce viable offspring could not be used in the claimed methods without experimentation to overcome the barriers to producing viable offspring using those cells. With regard to the quotation from Bradley *et al.* regarding the potential of ES cells from large animals, the potential of ES cells is not in dispute. The basis of the enablement rejection is that, at the time the instant application was filed, the potential of ES cells from mammals other than mice could not have been realized without undue experimentation.

Regarding Campbell *et al.*, Applicant argues, “[w]hile Campbell *et al.* indicate that ‘as yet there are no reports of any cell lines which contribute to germ line in any species other than mouse’, the reference does not conclude that ES cells cannot be isolated from species other than mice or provide evidence that would lead one skilled in the art to the conclusion that Applicants’ claimed method...cannot be practiced on any species other than mouse” (second full paragraph on page 6). However, as applicant points out in the fourth full paragraph on page 3, “The standard for enablement under 35 U.S.C. § 112, first paragraph, is whether the claimed invention can be practiced *without undue experimentation* given the guidance presented in the specification and what was known to the skilled artisan at the time the subject application was filed” (emphasis added). Applicant’s method cannot be practiced without a cell line that contributes to the germ line, and the fact that Bradley *et al.* had published their teaching of the potential advantages of ES cells for engineering large animals five years before the teachings of Campbell *et al.* were published clearly demonstrates that the level of experimentation required to produce

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viable offspring using ES cell technology in any mammalian species other than mouse is beyond what would be considered routine in the art.

In support of enablement for the full scope of the claims, Applicant cites three publications Thompson *et al.* (Paper No. 11, Exhibit 1), Cibelli *et al.* (Paper No. 11, Exhibit 2) and Iwasaki *et al.* (Paper No. 11, Exhibit 3) and contends that the teachings therein provide evidence that Applicant's specification enables one skilled in the art to make and use the full scope of the claimed invention of claims 1, 5, 8, 11, 14, 18, 21 and 41. Although each of cited publications report some progress in development of ES cell technology in mammals other than mice, each further teaches that significant work remains before ES cell technology will become routine in the broad genus of all non-human mammals. Thompson *et al.* teaches only that ES cells obtained from rhesus monkey could be made to express cell surface markers consistent with embryonic germ layers *in vitro* and form complex tumors when injected into SCID mice (see the final paragraph on page 7846). Thompson *et al.* provide no evidence that the cells they describe could be used according to the methods of the instant application to produce a viable animal.

Cibelli *et al.* concludes, "[t]he results in this study indicate that, although genetic modifications could be made directly in bovine ES-like cells by microinjection, and transgenic cells could be selected by a standard neomycin resistance approach, limitations in the number of cells that can be microinjected, the slow growth of the cells, and our inability to clonally propagate the ES-like cells limits the usefulness of this approach, particularly for gene targeting" and "until germline transmission is demonstrated, we refer to our cells as 'pluripotent or ES-like cells'" (second and third full paragraphs on page 644). Cibelli *et al.* thus express skepticism

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regarding the usefulness of their technology in the routine production of viable and useful animals.

Iwasaki *et al.* demonstrate the production of chimeric bovine calves using a method comprising aggregation of “ES-like” cells with tetraploid bovine embryos. However, of the 6 calves produced, only two were chimeric and no chimeric cells were found in the gonadal tissue. Iwasaki *et al.* concludes, “[t]he results clearly indicate that the 137-cells are able to contribute to chimera formation, *but at a very low level*” (sentence bridging pages 474 and 475; emphasis added). In contrast to Applicant’s contention that Iwasaki *et al.* support the enablement of their method in mammalian species other than mouse, teachings therein actually indicate additional unpredictability in extending the because Iwasaki *et al.* found that the tetraploid cells in the embryos contribute to some or, in the case of 4 out of 6 animals, all of the tissues in the animal produced (see especially the second full paragraph on page 474). This is not the case in mice, where the cells of the tetraploid embryo are not found in the product animal (see Wang *et al.* cited in Paper No. 8).

The teachings cited by Applicant do not teach, nor do they suggest that it would be possible to practice the claimed method in any and all mammalian species. At best, the teachings of Cibelli *et al.* and Iwasaki *et al.* suggest that it might be possible to use the methods of the claimed invention to produce a wild-type chimeric bovine. However, as the chimeric animals produced have not been shown to be capable of germline transmission, the skilled artisan would not know how to use the chimeric bovine produced by the method in a practical application.

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Therefore, for the reasons of record in Paper No. 8 recited herein above, the skilled artisan would not be able to practice the invention of claims 1, 5, 8, 11, 14, 18, 21 and 41 without first engaging in undue experimentation.

Rejection of claim 44 under 35 U.S.C. § 112, first paragraph

Claim 44 has been rejected for reasons of record in Paper No. 8 as lacking enablement for a method of producing XO F1 ES cells from mammalian species other than mice.

Applicant's arguments filed in Paper No. 11 have been fully considered but they are not persuasive.

In response to the rejection, Applicant argues that the specification teaches a method of producing mammalian XO F1 ES cells and that a negative selection marker can be inserted onto the Y chromosome by homologous recombination using methods known and readily available and concludes that armed with the teachings of the specification and what was known to the skilled artisan at the time the subject application was filed it would have been a routine matter for one skilled in the art to produce mammalian XO F1 ES cells according to the full scope of the claim.

Again, it is important to point out that the teachings of the instant disclosure and prior art have only been reduced to practice in mice; therefore, teachings cited in Paper No. 11, are merely prophetic as they are applied to all mammalian species other than mice. As above, the foundation of the rejection is that the absence of useful ES cell technology in species other than mouse that would require the skilled artisan to exercise undue experimentation to practice the claimed invention.

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As in the case of the methods directed to production of a transgenic animal, Applicant argues that the references cited by the Examiner fail to support the conclusion that undue experimentation would be required to practice the invention in species other than mice. With regard to Bradley *et al.*, Applicant concedes that the reference teaches that in 1992, it had yet to be demonstrated that ES cells isolated from farm animal species can proliferate and differentiate in an embryo *in vivo* and contribute to somatic tissues or germ cells, but argues Bradley *et al.* “do not conclude that the ES cells isolated from farm animal species are not ES cells or that ES cells cannot be isolated from mammalian species other than mice. In fact, Bradley *et al.* indicate that ‘ES cells offer the same potential advantages for genetic engineering of large animals that have been realized in mice’” (first full paragraph on page 6). However, the skilled artisan would not know how to use an XO F1 ES cell produced according to the instant application if said XO F1 ES cell could not then be used to make a transgenic animal. Thus, as argued above, enablement for the method requires more than cells that can proliferate *in vitro*, it requires that the ES cells “proliferate and differentiate in an embryo *in vivo*”. The skilled artisan would not know how to use XO F1 ES cells having all of the properties of an ES cell except for the ability to produce viable offspring without experimentation to overcome the barriers to producing viable offspring using those cells. With regard to the quotation from Bradley *et al.* regarding the potential of ES cells from large animals, the potential of ES cells is not in dispute. The basis of the enablement rejection is that, at the time the instant application was filed, the potential of XO F1 ES cells from mammals other than mice could not have been realized without undue experimentation.

As above, with regard to Campbell *et al.* Applicant argues, “[w]hile Campbell *et al.* indicate that ‘as yet there are no reports of any cell lines which contribute to germ line in any

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species other than mouse', the reference does not conclude that ES cells cannot be isolated from species other than mice or provide evidence that would lead one skilled in the art to the conclusion that Applicants' claimed method...cannot be practiced on any species other than 'mouse' (second full paragraph on page 6). The skilled artisan would not know how to use Applicant's method without a cell line that contributes to the germ line because the specification and prior art provide no use for an XO F1 ES cell other than the production of a transgenic animal. The fact that Bradley *et al.* had published their teaching of the potential advantages of ES cells for engineering large animals five years before the teachings of Campbell *et al.* were published clearly demonstrates that the level of experimentation required to produce viable offspring using ES cell technology in any mammalian species other than mouse is beyond what would be considered routine in the art.

Applicant again cites Thompson *et al.*, Cibelli *et al.* and Iwasaki *et al.* to support the enablement of the claims; contending that the teachings therein provide evidence that Applicant's specification enables one skilled in the art to make and use the full scope of the claimed invention of claim 44. As described above, although each of cited publications report some progress in development of ES cell technology in mammals other than mice, each further teaches that significant work remains before ES cell technology will become routine in the broad genus of all non-human mammals

Thompson *et al.* teaches only that ES cells obtained from rhesus monkey could be made to express cell surface markers consistent with embryonic germ layers *in vitro* and form complex tumors when injected into SCID mice (see the final paragraph on page 7846). Thompson does not suggest that the ES cells could be used to make a transgenic animal according to the

teachings of the instant application or prior art. Therefore Thompson *et al.* does not support a use for XO F1 ES cells from any mammal other than a mouse.

Cibelli *et al.* concludes, “[t]he results in this study indicate that, although genetic modifications could be made directly in bovine ES-like cells by microinjection, and transgenic cells could be selected by a standard neomycin resistance approach, limitations in the number of cells that can be microinjected, the slow growth of the cells, and our inability to clonally propagate the ES-like cells limits the usefulness of this approach, particularly for gene targeting” and “until germline transmission is demonstrated, we refer to our cells as ‘pluripotent or ES-like cells’ (second and third full paragraphs on page 644). Cibelli *et al.* thus express skepticism regarding the usefulness of their technology in the routine production of viable and useful animals. In addition, the teachings of Cibelli indicate that bovine ES cells are difficult to manipulate *in vitro* and cannot be cloned, which would be required to practice the claimed method.

Iwasaki *et al.* demonstrate the production of chimeric bovine calves using a method comprising aggregation of “ES-like” cells with tetraploid bovine embryos. However, of the 6 calves produced, only two were chimeric and no chimeric cells were found in the gonadal tissue. Iwasaki *et al.* concludes, “[t]he results clearly indicate that the 137-cells are able to contribute to chimera formation, *but at a very low level*” (sentence bridging pages 474 and 475; emphasis added). It is again worth noting that the teachings of Iwasaki *et al.* indicate additional unpredictability in extending the method to mammalian species other than mice because Iwasaki *et al.* found that the tetraploid cells in the embryos contribute to some, and in the case of 4 out of 6 animals all, of the tissues in the animal produced (see especially the second full paragraph on

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page 474). This is not the case in mice, where the cells of the tetraploid embryo are not found in the product animal (see Wang *et al.* cited in Paper No. 8).

Therefore, for the reasons of record in Paper No. 8 recited herein above, the skilled artisan would not be able to practice the invention of claim 44 without first engaging in undue experimentation.

New Grounds for Rejection

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-48 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-48 of copending Application No. 09/957,659. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-13, 21-26, 31-34, 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *wild-type* or XO mouse produced by a method wherein pluripotent ES cells are introduced into a tetraploid blastocyst of a mouse under conditions that result in production of an embryo and the resulting embryo is transferred into a foster mother which is maintained under conditions that result in development of live offspring, or a *wild-type* or XO embryo produced from a mouse tetraploid blastocyst having incorporated therein mouse non-inbred ES cells, does not reasonably provide enablement for any and all mice, mammals or mouse embryos produced according to the methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention: The claims are directed to a non-human mammal, mouse and embryo produced by the disclosed methods.

Breadth of the claims: The claims encompass any and all non-human mammals, mice, or embryos produced by the method of the instant invention regardless of the genotype or phenotype of said non-human mammal, mouse or embryo. The specification provides that the non-human mammals and mice obtained can be used to screen drugs that inhibit the occurrence or reverse a condition caused by or associated with a genetic alteration created in said non-human mammal or mouse (see especially page 11, lines 24-29).

State and Level of predictability in the art: The prior art teaches that the phenotype obtained with one species of transgenic animal is not predictive of the same phenotype in another species of transgenic animal. When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (Sigmund (2000) *Artrioscler. Thromb. Vasc. Biol.* 20:1425-1429, page 1425, paragraph 1). Further, transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (Wall (1996) *Theriogenology* 45:57-68). Still further, the particular genetic elements required for optimal expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall; *supra*).

Within mice the phenotype arising from insertion or deletion of even a well-characterized gene is equally unpredictable. Doetchman (1999) *Lab. Animal Sci.* 49:137-143 teaches, “[o]ne often hears the comment that genetically engineered mice...are not useful because they frequently do not yield the expected phenotype, or they don’t seem to have any phenotype. These

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expectations are often based on years of work, and in some instances, thousands of publications of mostly in vitro studies” (page 137, paragraph 1). Doetchman goes on to teach, “it has become clear that genetic background plays an important role in the susceptibility of mice to many disorders. Therefore, the phenotypes of knockout mouse strains will also have genetic background dependencies” (page 140, column 2, third full paragraph) and “[a]pparent lack of phenotype more likely reflects or inability to ask the right questions, or our lack of tools to answer them” page 142, first paragraph. These teachings point out that the phenotype arising from any given mutation or genetic manipulation of a transgenic mouse is highly unpredictable and in some cases requires empirical experimentation to uncover.

Amount of direction provided by the inventor: The disclosure provides detailed guidance as to how to establish mouse F1 XY ES cell lines and how to obtain XO ES cells from said mouse F1 XY ES cell lines. The specification also provides a description and reduction to practice of a wildtype mouse. The specification is silent regarding how to use any and all non-human mammals beyond a general statement that they can be used to screen drugs.

Existence of working examples: Although the use of transgenic mice as disease models and for the purpose of screening potential pharmaceuticals is well known in the art and the art provides many working examples, in order to use any given animal the skilled artisan must have a means to measure the phenotype of that particular animal and changes in that phenotype. The means to measure any given phenotype is unique to that phenotype and there does not exist a general means to assess a change in phenotype. Working examples provided in the prior art cannot, therefore, be globally extended to any and all phenotypes.

Relative skill of those in the art: Although the level of skill in the art is high, production of a useful phenotype through expression or knockout of a given gene in all species of mammal, or expression or knock out of any and all genes in the mouse is beyond the capabilities of the ordinary skilled artisan.

Quantity of experimentation needed to make or use the invention: Given the unpredictability of the phenotype obtained by insertion or deletion of any gene in the genome of an animal, the skilled artisan would have to engage in undue experimentation to identify a use for any and all mutant mice made by the methods of the instant Application. The skilled artisan is therefore unable to make and use the claimed invention without undue experimentation.

Claim 40 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

The claim is directed to a method of identifying a candidate drug to be administered to treat a condition in a mammal, comprising producing a mutant mouse that is a model of the condition and administering to said mutant mouse a drug to be assessed, and thus encompasses a method of using any and all mutant mice to identify a candidate drug.

In response to the arguments of record in Paper No. 8, Applicant argues that methods of using mice as models of disease in other mammals is routine in the art. Therefore, any mouse *established to be a phenotypic model of a mammalian disease* can be used according to the claim to screen for candidate drug to be administered to treat a condition. However, the claim covers

much more than this. Applicants arguments are not commensurate in scope with the scope of the claim.

However, for the reasons provided in detail herein above, the phenotype arising from any given mutation in a transgenic mouse is highly unpredictable. Therefore, although the use of transgenic mice as disease models for the purpose of screening potential pharmaceuticals is well known in the art and the art provides many working examples, in order to use any given animal the skilled artisan must have a means to measure the phenotype of that particular animal and changes in that phenotype. The means to measure any given phenotype is unique to that phenotype and there does not exist a general means to assess a change in phenotype. Working examples provided in the prior art cannot, therefore, be globally extended to any and all phenotypes.

Again, although the level of skill in the art is high, the skilled artisan would not be able to practice the claimed invention without first establishing a mouse having a phenotype that could be used as a model for a mammalian disease. Given the art recognized unpredictability of phenotype arising from any given mutation and the failure of the instant disclosure to provide a single example of a disease model produced according to the instant method, the skilled artisan would not be able to practice the claimed invention without first engaging in undue experimentation to establish a disease model.

Claims 1, 4, 8, 9, 15, 21, 22 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a mouse wherein ES cells are introduced into tetraploid blastocysts and a mouse produced by the method, to the extent

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the mouse is enabled by the disclosure according to the scope of enablement rejection contained herein above, does not reasonably provide enablement for a method of producing any animal from any pluripotent cell other than an ES cell or for any animal produced from any pluripotent cell other than an ES cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims.

The claims encompasses methods of making a mouse comprising: introducing any pluripotent cell into a tetraploid blastocyst. To date, the relevant art only teaches production of mice from tetraploid blastocysts using ES cells (see Wang *et al.* (1997; cited in Paper No. 8)). Although Iwasaki *et al.* (*supra*) teach the inefficient production of a chimeric bovine from a tetraploid blastocyst using “ES-like” cells, for the reasons provided in the response to arguments herein above, the skilled artisan would not be able to apply the teachings of Iwasaki *et al.* to a practical utility without first engaging in undue experimentation. The prior art does not provide a single example of a useful animal being produced according to the claimed method from any cell other than an ES cell; therefore the skilled artisan must depend upon the teachings of the instant disclosure to provided detailed guidance as to how to practice the invention using pluripotent cells other than ES cells. The specification is silent, however, with respect to how to make a useful animal using any cell other than a mouse ES cell.

Although the relative level of skill in the art is high, because neither the prior art nor the instant disclosure provide any guidance as to how to produce a useful mouse according to the teachings of the disclosure and prior art from a cell other than an ES cell, the skilled artisan would not know how to make a mouse using any cell other than an ES cell. One of ordinary skill

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in the art would therefore have to engage in undue experimentation in order to develop methods of producing a mouse using the methods disclosed in the instant application from a cell other than an ES cell.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19, 25 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19, and 20, 25 and 26 as they depend from claim 19, are indefinite in its recitation of "the mutant non-human mammal is a mouse". There is no antecedent basis for a non-human mammal in claim 18, from which claim 19 depends, which is directed to a method of producing a non-human mammalian *embryo*.

Claims 25 and 26 are also indefinite in that they are directed to a mutant mouse embryo for which there is no antecedent basis in claim 19. Amending claim 19 to correct the antecedence problem described above would also overcome this rejection.

Claim 47 is indefinite in its recitation of "the non-inbred male ES cell", as claim 46, from which claim 47 depends, is limited to "non-inbred *mouse* ES cells".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Note: The following rejection applies to the extent that the prior art discloses the same compositions and/or method embraced by the instant invention. The prior art rejection is not to be construed as an indication that the claimed or anticipated methods are *enabled* for the wide breadth of subject matter potentially embraced by the claims. The compositions and/or methods disclosed in the prior art are essentially enabled to the same extent as the instant specification, since there is no significant difference in the level of guidance presented in either case.

Claims 1-3, 8-12, 14-16, and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang *et al.* (1997; cited in Paper No. 8).

Claims 1-3 are directed to a method of producing a non-human mammal wherein pluripotent cells are introduced into tetraploid blastocysts of the same mammalian species under conditions that result in production of an embryo and the resulting embryo is transferred into a foster mother which is maintained under conditions that result in development of live offspring. Claim 2 limits the non-human mammal to a mouse and claim 3 limits the pluripotent cells to ES cells and the introducing step to injection.

Wang *et al.* teaches a method of producing a non-human mammal wherein pluripotent cells are introduced into tetraploid blastocysts of the same mammalian species under conditions that result in production of an embryo and the resulting embryo is transferred into a foster mother which is maintained under conditions that result in development of live offspring (see especially the second full paragraph on page 144 and Table 2 and the caption thereto). Wang *et al.* also

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teaches a non-human mammal that is a mouse, pluripotent cells that are ES cells and an introducing step that comprises injecting the ES cells into the blastocyst.

Claims 8-10 are directed to a non-human mammal or mouse produced according to the method of claims 1-3 respectively. As the methods of claims 1-3 are anticipated by Wang *et al.* so too are the products of those methods.

Claims 14-16 are directed to a method of producing a mutant non-human mammal, wherein pluripotent cells comprising at least one mutation are introduced into tetraploid blastocysts of the same mammalian species under conditions that result in production of an embryo and the resulting embryo is transferred into a foster mother which is maintained under conditions that result in development of live offspring. Claim 14 limits the non-human mammal to a mouse and claim 16 limits the pluripotent cells to ES cells and the introducing step to injection. It is clear from the Markush group set forth in claim 33 that the definition of mutation includes random mutation. Because random mutation is a natural process that would certainly have occurred in the ES cells used by Wang *et al.*, the limitation of “comprising at least one mutation” is met by the ES cells of Wang *et al.*; therefore, the claims are anticipated by Wang *et al.* for the reasons set forth above regarding claims 1-3.

Claims 21-23 are directed to a mutant mouse produced according to the methods of claims 14-16 respectively. As the methods of claims 14-16 are anticipated by Wang *et al.* so too are the products of those methods.

The method of producing a non-human mammal or mouse, or mutant non-human mammal or mouse and products produced by those methods taught by Wang *et al.* are the same

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as those taught in the instant application; therefore the limitations of the claims are met by Wang *et al.*

Claims 1, 2, 8, 9, 14, 15, 21, 22, 27, 31, 33, 35, 38 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Ueda *et al.* (1995) *Exp. Anim.* 44:205-210 as evidenced by Yagi *et al.* (1993) *Anal. Biochem.* 214:70-76.

The limitations of claims 1, 2, 8, 9, 14 and 15 are set forth herein above.

Ueda *et al.* teaches a method of producing a non-human mammal wherein pluripotent cells are introduced into tetraploid blastocysts of the same mammalian species under conditions that result in production of an embryo and the resulting embryo is transferred into a foster mother which is maintained under conditions that result in development of live offspring according to claim 1 (see especially beginning the final paragraph on page 206 and continued through the second full paragraph on page 207, and Table 1 and the caption thereto). Ueda *et al.* also teaches a non-human mammal that is a mouse according to claim 2.

Claims 8 and 9 are directed to a non-human mammal or mouse produced according to the method of claims 1 and 2 respectively. As the methods of claims 1 and 2 are anticipated by Ueda *et al.* so too are the products of those methods.

Again, because random mutation is a natural process that would certainly have occurred in the ES cells used by Ueda *et al.*, the limitation of "comprising at least one mutation" is met by the ES cells of Ueda *et al.*; therefore, claims 14 and 15 are anticipated by Ueda *et al.* for the reasons set forth above regarding claims 1 and 2.

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Claims 21 and 22 are directed to a mutant mouse produced according to the methods of claims 14 and 15 respectively. As the methods of claims 14 and 15 are anticipated by Ueda *et al.* so too are the products of those methods.

Claim 27 is directed to a method of producing a mutant mouse comprising: (a) introducing mouse non-inbred ES cells comprising at least one mutation in genomic DNA into mouse tetraploid blastocysts; maintaining the product of (a) under conditions that result in production of embryos; (c) introducing an embryo into a pseudopregnant female; and (d) maintaining the female into which the embryo is introduced under conditions that result in development of live offspring.

As described above regarding claims 1 and 14, Ueda *et al.* teaches each of the limitations of the claimed method. Ueda additionally reduces the method to practice using TT2 ES cells, which are non-inbred ES cells (see Yagi *et al.*, page 71, second paragraph in column 2).

Claims 31 and 33 are directed to a mouse embryo produced from a mouse tetraploid blastocyst having incorporated therein mutant mouse non-inbred ES cells. Claim 31 additionally limits the embryo to an embryo wherein the mutant mouse non-inbred ES cells comprise random mutations. As described above, Ueda *et al.* teach a method of producing a mutant mouse comprising the step of producing an embryo by introducing mutant mouse non-inbred ES cells, which are randomly mutated via natural processes, into a mouse tetraploid blastocyst. The embryo produced in this intermediate step meets the limitations of the claims.

Claim 35 is directed to a method of producing a mutant mouse comprising each of the limitations of claim 27 but not limited to an ES cell comprising at least one mutation. As the method of Ueda *et al.* teaches all of the limitations of the narrower embodiment, it also meets the

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limitations of the broader claim 35. Likewise, claim 38 is directed to a mouse embryo having all of the limitations of the embryo of claim 31 but not limited to an embryo produced from mutant mouse ES cells. As the embryo of Ueda *et al.* comprises all of the limitations of the narrower embodiment, it also meets the limitations of the broader claim 38.

Claim 41 is directed to a method of producing a mutant non-human mammal, wherein pluripotent cells comprising at least one mutation in genomic DNA are introduced into tetraploid blastocysts of the same mammalian species under conditions that result in production of an embryo and the resulting embryo is transferred into a foster mother which is maintained under conditions that result in development of live offspring, wherein the pluripotent cells are non-inbred pluripotent cells. As described herein above, each of the limitations of the claim are taught by Ueda *et al.*

The method of producing a non-human mammal or mouse or embryo, or mutant non-human mammal or mouse or embryo and products produced by those methods taught by Ueda *et al.* are the same as those taught in the instant application; therefore the limitations of the claims are met by Ueda *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18, 19, 25, 27, 28, 35, 36 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uchida *et al.* (1995) *Anim. Sci. Technol.* 66:361-367 as evidenced by Yagi *et al.* (*supra*) in view of either one of Ueda *et al.* (*supra*) or Wang *et al.* (*supra*).

Claims 18 and 19 directed to a method of producing a mutant non-human mammalian embryo comprising injecting mutant non-human non-inbred ES cells into non-human tetraploid blastocysts and maintaining the resulting tetraploid blastocysts under conditions that result in formation of embryos. Claim 19 limits the non-human non-inbred ES cells to mouse cells. Claim 25 is directed to a mutant mouse embryo produced according to the method of claim 19.

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Claims 27 and 28 are directed to a method of producing a mutant mouse comprising: (a) introducing mouse non-inbred ES cells comprising at least one mutation in genomic DNA into mouse tetraploid blastocysts; maintaining the product of (a) under conditions that result in production of embryos; (c) introducing an embryo into a pseudopregnant female; and (d) maintaining the female into which the embryo is introduced under conditions that result in development of live offspring. Claim 28 further limits the method to a method wherein (a) introducing is carried out by injection.

Claims 35 and 36 are directed to a method having all of the limitations of claims 27 and 28, but not limited to an ES cell comprising at least one mutation.

Claim 45 is directed to an XO female mouse produced by introducing XO F1 ES cells into tetraploid mouse blastocysts under conditions that result in production of an embryo and transferring the resulting embryo into a foster mother which is maintained under conditions that result in development of live offspring.

Uchida *et al.* teaches producing a non-human mammalian embryo comprising injecting non-human (i.e. mouse) non-inbred (i.e. TT2) ES cells into non-human blastocysts and maintaining the resulting blastocysts under conditions that result in formation of embryos. For the reasons provided herein above, the ES cells of Uchida *et al.* meet the limitation of mutant. Uchida *et al.* further teaches the method wherein the ES cells used are XO F1 ES cells.

Uchida *et al.* teaches all of the limitations of the claimed methods except for the use of tetraploid blastocysts.

Ueda *et al.* teaches production of mice derived entirely from mouse TT2 ES cells by (a) introducing TT2 ES cells into tetraploid mouse blastocysts under conditions that result in

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production of an embryo; and (b) transferring the resulting embryo into a foster mother which is maintained under conditions that result in development of live offspring (see especially *Coculture of ES cells with tetraploid embryos and embryo transfer*, beginning the second column of page 206 and continued the first column of page 207).

Wang *et al.*, like Ueda, teaches production of mice entirely from embryonic stem cells by introducing ES cells into tetraploid mouse blastocysts under conditions that result in production of an embryo and transferring the resulting embryo into a foster mother which is maintained under conditions that result in development of live offspring (see especially *Morula aggregation and blastocyst injection* in column 1 of page 144).

The teachings of Uchida *et al.* show that the means to make XO F1 ES cells capable of producing a viable mouse and a line of such cells were known in the art at the time of filing of the instant Application. The teachings of Wang *et al.* and Ueda *et al.* show that a method of making a mouse entirely derived from cultured ES cells by introducing ES cells into a tetraploid blastocyst was also known in the art at the time the instant application was filed. It would have been obvious to one of ordinary skill in the art to combine the teachings of Uchida *et al.* and Ueda *et al.* or Wang *et al.* according to the methods of the instant application and to produce the claimed XO female mouse, as the teachings provide the means to make XO F1 ES cells from the TT2 cell line, a line of XO F1 ES cells derived from TT2 cells that is capable of generating viable mice, and the means to produce a mouse entirely derived from TT2 or other ES cells.

Motivation to combine these teachings comes from Wang *et al.* who teaches in the first paragraph of the second column on page 143, "the practical benefit of [production of mice from ES cells using tetraploid blastocysts] should be emphasized as it may save time and money for

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generating mutant mouse strains from cultured ES cells and allows a rapid access to mutant fetuses and mice, a potential advantage for many investigators in the field of mouse genetics". In the absence of evidence to the contrary, the skilled artisan would also have a reasonable expectation of success in combining the teachings of Uchida *et al.* with the teachings of Ueda *et al.* or Wang *et al.* This is particularly true in the case of Ueda *et al.* who demonstrate that the parental TT2 cell line from which the XO F1 ES cells of Uchida *et al.* is derived can be used in their method of making a mouse.

Conclusion

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
December 13, 2002

Anne-Marie Falk
ANNE-MARIE BAKER
PATENT EXAMINER